CHRONIC TOXICITY SUMMARY

CHLOROPICRIN

(trichloronitromethane; nitrochloroform; nitrochloromethane)

CAS Registry Number: 76-06-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.4 µg/m^3** (0.05 ppb)
Critical effect(s)	Nasal rhinitis and bronchiectasis in mice
Hazard index target(s)	Respiratory system

II. Chemical Property Summary (from HSDB (1996) except as noted)

Description	Colorless to faint yellow liquid
Molecular formula	CCl_3NO_2
Molecular weight	164.4 g/mol
Boiling point	112°C
Melting point	–64°C (CRC, 1994)
Vapor pressure	5.7 torr @ 0°C (Fries and West, 1921); 3.2 kPa (24 torr) @ 25°C (Tomlin, 1994)
Solubility	1.6 g/L water @ 25°C; 2.272 g/L water @ 0°C 1.9 g/L water @ 20°C; miscible with benzene, ethanol, carbon disulfide, ether, carbon tetrachloride, acetone, methanol, acetic acid
Conversion factor	6.72 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Chloropicrin is used primarily as a preplant soil fumigant against insects and fungi; it also kills weed and grass seeds when applied to soil. Chloropicrin is occasionally used as a fumigant in grain elevators and storage bins (HSDB, 1996). Chloropicrin is used as an indicator chemical in other fumigants such as methyl bromide because of its potent irritant properties. Chloropicrin was used in World War I as a chemical warfare agent because of its potent activity as a lachrymator. Chloropicrin has a minor use in the chemical synthesis of methyl violet. Chloropicrin can also form in drinking water as a result of chlorination processes (Duguet *et al.*, 1985; Merlet *et al.*, 1985). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 1507 pounds of chloropicrin (CARB, 2000). This does not include emissions from its major use as a preplant soil fumigant, either alone or in combination with other fumigants, because agricultural field applications are not covered under the Air Toxics Hot Spots

program. Approximately 3,630,000 lbs. of chloropicrin were used in agriculture in California in 1999 (DPR, 2000).

IV. Effects of Human Exposure

No studies are available which describe toxic effects to humans from chronic exposure to chloropicrin. Human exposures to concentrations less than 1 ppm for very short periods of time are extremely irritating (ACGIH, 1992; Fries and West, 1921). The threshold of odor detection in humans is approximately 1 ppm (ACGIH, 1992).

V. Effects of Animal Exposure

Burleigh-Flayer and Benson (1995) conducted a chronic inhalation bioassay with CD rats (50-60 per sex per dose) exposed discontinuously to 0 (air), 0.1, 0.5, or 1.0 ppm 99.6% pure chloropicrin vapor 6 hours/day for 5 consecutive days/week over 107 weeks. Clinical signs (such as hypoactivity and decreased startle response) were increased in both sexes, primarily at 1.0 ppm. Increased mortality was noted in males at 0.5 and 1 ppm and in females at 1 ppm. Absolute and relative increased lung and liver weights and increased nasal rhinitis were reported in both sexes at the 1 ppm level. However, no effects were seen at 0.1 ppm. Thus this study yielded a NOAEL of 0.1 ppm (0.67 mg/m^3) for chronic non-cancer effects in rats.

Results from chronic inhalation of chloropicrin in rats (Burleigh-Flayer and Benson, 1995)

Chloropicrin	Lung wt., m	Lung wt., f	Rhinitis, m	Rhinitis, f	Mean survival, m
0	2.086 g	1.574 g	20/50	18/50	696 d
0.1 ppm	2.089 g	1.464 g	24/50	17/50	669 d
0.5 ppm	2.202 g	1.460 g	21/50	26/50	672 d*
1.0 ppm	2.448 g	1.633 g	35/50**	23/50	647 d**

*$p<0.05$; **$p<0.01$

A similar study in mice (Burleigh-Flayer *et al*., 1995) resulted in the same NOAEL. CD-1 mice (50/sex/dose) were exposed to chloropicrin (99.6% pure) vapor at 0 (air), 0.1, 0.5, or 1.0 ppm for 6 hours/day, 5 days/week for at least 78 weeks. Body weights and body weight gains were significantly decreased in both sexes at ≥ 0.5 ppm. Food consumption was decreased in males at 1.0 ppm and in females at ≥ 0.5 ppm. Absolute and relative lung weights were increased in a dose-related manner in both sexes at ≥ 0.5 ppm. Changes in pathology observed macroscopically in the 1.0 ppm males included increased numbers of lung nodules and increased numbers of kidney cysts. In females lung masses and kidney cysts were seen at 0.5 ppm. Microscopic pathology changes included increased nasal cavity lesions (including serous exudate, hyaline epithelial inclusions, rhinitis, olfactory and epithelial atrophy) and lung lesions (including alveolar protein deposits, alveolar histiocytosis, hemorrhage, peribronchiolar lymphocytic infiltrate, bronchiectasis, bronchial submucosal fibrosis, peribronchiolar smooth muscle hyperplasia), in addition to kidney cysts at ≥ 0.5 ppm (CDPR, 2000).

Results from chronic inhalation of chloropicrin in mice (Burleigh-Flayer *et al*., 1995)

Chloropicrin	Rhinitis, m	Rhinitis, f	Bronchiectasis, m	Bronchiectasis, f	
0	6/50	3/50	0/50	0/50	
0.1 ppm	7/50	6/50	3/50	5/50	
0.5 ppm	17/50**	18/50**	28/50**	28/50**	
1.0 ppm	35/50**	32/50**	41/50**	44/50**	

**p<0.01

Yoshida *et al*. (1987) exposed groups of 12 male Fischer 344 rats intermittently to 0, 0.37, 0.67, 1.58, or 2.93 ppm chloropicrin vapor 6 h/day, 5 days/week for 13 weeks. Mean body weights were reduced in the highest 2 exposure groups, and red blood cell count, hematocrit, and hemoglobin concentration were significantly increased in the 2.93 ppm group. The treatment-related histological lesions reported were degeneration and necrosis of the bronchial and bronchiolar epithelia at 2.93 ppm and hypertrophy of these epithelia at 1.58 ppm. Thus the primary target organ was the respiratory tract and the subchronic NOAEL was 0.67 ppm (4.5 mg/m^3). (Eyelid closure and decrease in motor activity were seen in all exposure groups only during exposure. No morphological changes were seen at 0.67 ppm, so the authors deemed the behavior changes minor and not toxicologically important.)

Male Swiss-Webster mice (group numbers ranging from 16-24) were exposed by inhalation to a single level of different sensory irritants including chloropicrin for 6 hours/day for 5 days; unexposed control groups had 8-10 mice (Buckley *et al.*, 1984). The exposure level for chloropicrin was 7.9 ppm, which approximated the level sufficient to cause a 50% decrease in respiratory rate in mice (RD_{50}) (Kane *et al.*, 1979). Half the exposed mice and half the control animals were terminated immediately after the exposures and the other half 72 hours after the last exposure. All were examined for respiratory tract lesions. Body weights of chloropicrin exposed animals were reduced 10-25% below controls, but increased to normal levels during the recovery period. Nasal exudate and distention of the abdomen were observed. "Moderate" lesions, characterized by exfoliation, erosion, ulceration, or necrosis, were observed in the respiratory and olfactory epithelium, and minimal inflammation and squamous metaplasia were observed in the respiratory epithelium alone. Moderate to severe damage to the lower respiratory tract was described as "fibrosing peribronchitis and peribronchiolitis". Exfoliation, hyperplasia, and squamous metaplasia were also noted.

Condie *et al.* (1994) conducted a study of the toxicity of chloropicrin by oral exposure in Sprague-Dawley rats. Ten and ninety-day studies were conducted by dosing animals daily with chloropicrin in vehicle (corn oil) at a volume of 1 ml/kg. Groups of 10 rats/sex/group were dosed with 0, 10, 20, 40, and 80 mg/kg for the 10-day study and with 0, 2, 8, and 32 mg/kg for the 90-day study. Parameters examined included mortality, body weight, food and water consumption, hematology, serum clinical chemistry, and gross pathology and histology of organs. Only the high-dose group and the control group animals from the 90-day study were examined histopathologically. In the 90-day study, 6 males and 2 females in the 32 mg/kg dose group and 1 male and 3 females in the 8 mg/kg dose group died before the scheduled termination time. The authors noted signs of pulmonary complications (inflammation and congestion) in the dead animals. Previously, the animals had shown signs of respiratory distress, including wheezing and dyspnea. The deaths were considered to be exposure related and most likely due

to aspiration of chloropicrin. Among the survivors, mean body weight, hemoglobin levels, and hematocrits were significantly reduced in males in the 32 mg/kg dose group. Absolute thymus weights were reduced in female rats at 32 mg/kg, and female rats in the 8 mg/kg dose group showed decreased white blood cell count. Most animals in the 32 mg/kg dose group (>60%) showed histopathological changes in the forestomach including chronic inflammation, acantholysis, and hyperkeratosis. The authors considered the NOAEL to be 8 mg/kg/day.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Burleigh-Flayer and Benson (1995)
Study population	CD-1 mice (60 per sex per dose)
Exposure method	Discontinuous inhalation (0, 0.1, 0.5 or 1.0 ppm)
Critical effects	Nasal rhinitis; bronchiectasis
LOAEL	0.5 ppm
NOAEL	0.1 ppm
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	107 weeks
BMC_{05}	0.042 ppm
Average experimental exposure	0.0075 ppm at the BMC_{05} (0.042 x 6/24 x 5/7)
Human equivalent concentration	0.0016 ppm at the BMC_{05} (gas with extrathoracic respiratory effects, RGDR = 0.21 based on MV = 0.044 L/min and SA(ET) = 3 cm^2)
LOAEL uncertainty factor	not needed in the BMC approach
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3 (since RGDR adjustment was made)
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.05 ppb (0.4 $\mu g/m^3$)

The data on bronchiecstasis incidence in male and female mice were combined and the chronic REL for chloropicrin was developed using the BMC approach. Of the several models tested, the Gamma MultiHit Model gave the best fit to the combined bronchiecstasis data (p = 0.9750). The MLE_{05} was 0.070 ppm and the BMC_{05} was 0.042 ppm. Use of time extrapolation to equivalent continuous exposure, an RGDR adjustment for the area of the respiratory tract affected, and a total uncertainty factor of 30 resulted in a chronic REL of 0.05 ppb (0.4 $\mu g/m^3$).

The chronic study in mice (Burleigh-Flayer *et al*., 1995) yielded the same NOAEL of 0.1 ppm as the chronic study in rats (Burleigh-Flayer and Benson, 1995). Use of the mouse data with the NOAEL/UF approach led to a cREL estimate of 0.1 ppb. Use of the rat data yielded a chronic REL estimate of 0.2 ppb by the NOAEL/UF approach.

As another comparison, the study of Yoshida *et al*. (1987) found a NOAEL in rats of 0.67 ppm for intermittent exposure for 13 weeks. This is equivalent to a continuous exposure of 120 ppb.

Use of an RGDR of 0.25 for rats and a total uncertainty factor of 100 (3 for subchronic, 3 for interspecies, and 10 for intraspecies) results in a REL estimate of 0.03 ppb (0.2 $\mu g/m^3$).

VII. Data Strengths and Limitations for Development of the REL

Significant strengths in the REL for chloropicrin include the duration of exposure (lifetime) in the key study, the multiple dose study design with adequate sample sizes, and the demonstration of a NOAEL in rats and mice. Major areas of uncertainty are the lack of adequate human exposure data, limited reproductive toxicity data, and the appropriateness of time extrapolation of concentrations that cause irritative effects such as rhinitis.

VIII. Potential for Differential Impacts on Children's Health

Chloropicrin is a respiratory irritant. Respiratory irritants often have steep dose-response curves. Thus use of the human intraspecies factor of 10 should result in a REL that adequately protects children. Exacerbation of asthma, which has a more severe impact on children than on adults, is a known response to some respiratory irritants. However, there is no direct evidence in the literature to quantify such a response to chloropicrin, or to quantify a differential effect of chloropicrin on infants or children. We are currently evaluating our risk assessment methodologies, in particular the intraspecies uncertainty factor (UF_H), for adequacy in protecting infants and children. While we have not so far identified any indications that the currently used UF_H of 10 might be less than adequate to protect infants and children, this possibility should be considered in evaluating any exposure situation involving chronic exposures of infants or children to chloropicrin.

IX. References

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